Psychophysiology, 33 (1996), 93–101. Cambridge University Press. Printed in the USA.

Timing and amplitude of saccades during predictive saccadic tracking in schizophrenia

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Abstract

Schizophrenia patients have ocular motor abnormalities. It has been hypothesized that these abnormalities are associated with frontal eye field pathology. If so, schizophrenia patients should have difficulties decreasing saccadic reaction times in response to predictably moving targets. To evaluate the frontal eye field hypothesis, 25 schizophrenic and 26 nonpsychiatric subjects completed predictive saccadic tracking tasks. The groups demonstrated equivalent decreases in saccadic reaction times over consecutive trials. Schizophrenia patients, however, had faster reaction times and shorter amplitude saccades than nonpsychiatric subjects. The shorter amplitude saccades were made regardless of reaction time, perhaps an antipsychotic medication effect. The reaction time results are unlikely to be an effect of treatment with antipsychotic medication and are inconsistent with the hypothesis that schizophrenia patients have frontal eye field pathology.

Descriptors: Schizophrenia, Saccades, Predictive saccadic tracking

Numerous reports exist of ocular motor abnormalities among schizophrenia patients (Abel, Levin, & Holzman, 1992; Clementz & Sweeney, 1990). Knowledge of the ocular motor system's neural circuitry allows us to generate hypotheses about potential areas of neuropathology underlying eye movement abnormalities, a research strategy that may be applied to studying schizophrenia. For instance, it has been hypothesized that the eye movement anomalies observed among schizophrenia patients are due to frontal lobe pathology. More specifically, it has been suggested that the failure to modulate accurately appropriate saccades and to inhibit extraneous saccades among schizophrenia patients may be due to dysfunction in frontal eye fields (FEF) (Levin, 1984).

Although the FEF may be involved in the generation of most saccades (Bruce, Goldberg, Bushnell, & Stanton, 1985; Fox, Fox, Raichle, & Burde, 1985; Goday, Luders, Dinner, Morris, & Wylie, 1990; Melamed & Larsen, 1979; Segraves & Park, 1993), this brain region may be particularly important for accurate performance during more complex volitional saccade tasks (Leigh & Zee, 1991, p. 211; Pierrot-Deseilligny, 1994; Segraves & Park, 1993). For instance, FEF lesions alone have minor, if any, long-term effects on visually guided refixation saccades (Schiller, Sandell, & Maunsell, 1987; Schiller, True, & Conway 1980) but result in lasting and severe problems with memory-guided saccades (Deng, Goldberg, Segraves, Ungerleider, & Mishkin, 1986). Single cell recordings also reveal FEF neurons that discharge before purposive saccades in the absence of visual targets (Bruce & Goldberg, 1985). Performance abnormalities associated with FEF pathology among schizophrenia patients, therefore, might be most effectively elicited during more complex volitional saccade tasks.

In this regard, saccadic tracking elicited by predictably moving targets is one potentially intriguing paradigm. During one variation of such tasks, the target alternates at a constant rate between the same two peripheral locations ("square wave" stimulus), and subjects are instructed to maximize fixation time on the target. Normal subjects rapidly decrease their saccadic reaction times over consecutive trials, indicating that they have learned to predict the timing of target onset (Crawford, Goodrich, Henderson, & Kennard, 1989; Ross & Ross, 1987; Smit & Van Gisbergen, 1989; Tian, Zee, Lasker, & Folstein, 1991). After a few cycles, target appearance is typically anticipated and saccade generation often occurs before the actual target relocation.

Predictive saccade paradigms like these may be varied by manipulating the time between current fixation point offset and new target location onset. During a "regular" version, the offset of the current fixation point is simultaneous with the onset of the new target. During a "gap" version, the offset of the current fixation point precedes the onset of the new target location by some fixed time interval (e.g., 250 ms during which the screen is blank). During an "overlay" version, the target locations are continually illuminated, and subjects are cued to move by a periodic change in the colors of the targets. During all three variations, the location and timing of new target onset are always

This work was supported by grants from the United States Public Health Service (MH49906, MH42228, and MH51129).

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predictable. Gaps result in significantly reduced reaction times and overlays (like overlaps) may result in increased reaction times in comparison with the regular condition (see Fisher & Weber, 1992).

Predictive saccadic tracking tasks incorporate timing, anticipation, and accuracy. Accurate performance during these tasks is believed to depend on intact FEF (Leigh & Zee, 1991, p. 211). Bruce and Borden (1986) reported that monkeys presented with a gap square wave tracking task decreased their saccadic reaction times over consecutive trials like humans. After FEF lesions, however, the monkeys did not show this effect. Sharpe (1986) found that humans with frontal lesions had increased saccadic latencies and decreased saccadic amplitudes during square wave tracking, despite normal latencies and amplitudes of refixation saccades. Dorsolateral frontal cortex (which includes FEF) lesions resulted in a decreased frequency of anticipatory (reduced reaction time) saccades to predictable targets (Braun, Weber, Mergner, & Schulte-Monting, 1992). The extant data, therefore, suggest that dorsolateral frontal cortex (particularly FEF) supports normal performance during predictive saccadic tracking.

The few studies that have assessed predictive saccadic tracking among schizophrenia patients are inconclusive. Hommer, Clem, Litman, and Pickar (1991) reported that 20% of their schizophrenia patients did not learn to anticipate target motion during 10 cycles of a gap square wave task. The criterion for learning to anticipate consisted of early responses (between 500 ms before and 100 ms after target appearance) on four consecutive trials. Hommer et al. (1991) suggested that failure of a subset of schizophrenia patients to meet this criterion indicated "a severe level of impairment" (p. 788). In addition, patients medicated with antipsychotic drugs produced more hypometric saccades compared with nonmedicated patients and nonpsychiatric subjects.

Clementz, McDowell, and Zisook (1994) reported that schizophrenia patients learned to anticipate target motion as well as nonpsychiatric comparison subjects during 12 cycles of a regular square wave task. The 12 cycles were divided into three successive blocks (4 cycles each) with average reaction times calculated per block. The criterion for learning to anticipate target motion was a decrease in reaction time over blocks. Schizophrenia patients and nonpsychiatric subjects demonstrated similar decreases in reaction time over blocks. In addition, the patients (most of whom were medicated) produced slightly hypometric rightward-going saccades during the task.

Both of these studies reported short amplitude saccades among medicated schizophrenia patients. The studies appear to conflict on whether or not schizophrenia patients learn to anticipate target motion. The divergent results may arise from a number of factors, including the differences in the criteria used to measure anticipation and the type of square wave task presented. Unfortunately, data to help us resolve this discrepancy are not presently available.

To help clarify this issue, schizophrenia and nonpsychiatric subjects were presented with three variations of a square wave task: regular, gap, and overlay. A regular task was used in an attempt to replicate the Clementz et al. (1994) results. A gap task was used to help determine whether the differences between the Hommer et al. (1991) and Clementz et al. (1994) results were due to differences in stimulus characteristics. An overlay task was used to help address Hommer et al.'s (1991) hypothesis that hypometric saccades during predictive saccadic tracking among schizophrenia patients were due to "an inadequacy of provisional/short-term or working memory" (p. 788; see also Goldman-Rakic, 1987). According to this hypothesis, the overlay condition should eliminate hypometric saccades by circumventing schizophrenia patients' reliance on "dysfunctional" working memory (because the new target location was always visible).

In addition to the predictive tracking tasks, subjects completed two tasks requiring the generation of unpredictable, visually guided refixation saccades. First, subjects completed a centrifugal/centripetal task. Dysfunction of the saccade-related regions of the cerebellum results in a characteristic pattern of hypometric centrifugal and hypermetric centripetal saccades (Leigh & Zee, 1993, p. 107; Ritchie, 1976). If schizophrenia patients show this pattern, then cerebellar dysfunction could not be ruled out as a potential cause of abnormalities of saccadic amplitude among these subjects.

Second, a "midpoint" saccade task was presented during which subjects generated saccades between horizontal target locations equidistant from central fixation (what Becker [1989, p. 23] called "symmetric saccades across the primary position," stimuli that are optimal for assessing saccade metrics). This task provided a basis of comparison for more accurately evaluating subjects' square wave tracking performance. The midpoint and predictive tasks were similar (both required saccade generation to targets equidistant from central fixation), although the former task lacked the predictive component of the latter task. If the schizophrenia patients performed deviantly on the midpoint task, we could not rule out a more ubiquitous problem with saccadic generation among these subjects.

We hypothesized that schizophrenia patients would perform normally on the refixation tasks (see, e.g., Clementz et al., 1994; Fukushima et al., 1988, 1990). During predictive saccadic tracking, however, FEF pathology among schizophrenia patients should result in (a) the inability to reduce saccadic reaction time over trials (Bruce & Borden, 1986), (b) the generation of hypometric saccades (Sharpe, 1986), and (c) the production of few saccades anticipating target movement (Braun et al., 1992).

Method

Subjects

Twenty-five patients with DSM-III-R schizophrenia (American Psychiatric Association, 1987) and 26 nonpsychiatric comparison subjects participated in this study. Subjects were evaluated using the Structured Clinical Interview for DSM-III-R diagnoses (Spitzer, Williams, Gibbon, & First, 1988). Participants were in good physical health, absent of known neurological hard signs (including observable motor tremor), not taking anxiolytics (except for one patient; see below) or sedative-hypnotics, and free from current psychoactive substance use disorders. All participants provided informed consent.

Schizophrenia patients. Patients (median age = 38, 25th–75th percentile = 31–45, 28% female) were recruited from inpatient and outpatient psychiatric facilities associated with UCSD. Patients who passed the screening procedures were entered into the study as they became available. They were rated on the Global Assessment of Functioning Scale (Axis V of DSM-III-R) on the day of testing (median = 33, 25th–75th percentile = 31–45). At the time of testing, 20 patients were on various doses of antipsychotic medications (median CPZ equivalent dose = 300 mg, 25th–75th percentile = 100–500; Kaplan, Sadock, & Grebb, 1994), 10 patients were on various doses of anticholinergic med-

ications, and 2 patients were on low doses of antimanic medications (1 on lithium and 1 on klonopin). The inclusion of the two patients on antimanic medications did not affect the pattern of results (either means or variances) reported below.

Nonpsychiatric subjects. Nonpsychiatric subjects (median age = 34.5, 25th–75th percentile = 26–50, 54% female) were recruited through local advertisements. They were evaluated with the SCID and MMPI-2 (Hathaway & McKinley, 1989), and were screened for a history of psychiatric disorders among their first-degree biological relatives. Only subjects without a major affective disorder, psychotic disorder, an elevation (T score > 70) on MMPI-2 scales L, F, 2, 6, 7, or 8, or a family history of psychotic disorder, suicide, or psychiatric hospitalization were asked to participate.

Apparatus

Ocular motor recordings were obtained in a quiet, darkened (<0.1 cd/m^2) room. Horizontal eye movements were measured from both eyes using an Eye Trak Model 210 eye movement monitor and infrared spectacles (4 ms time constant) mounted on eyeglass frames (Applied Science Laboratories, Waltham, MA). Subjects' heads were stabilized using a bite bar.

Stimuli were presented on a high-resolution Zenith flat-surface color monitor (model ZCM-1492) positioned 37 cm from the subject's eyes. Eye movement recordings were digitized at 256 Hz using a Data Translation (DT2821) A-to-D board connected to an IBM-compatible computer. Recordings were displayed on a video screen so performance could be monitored continuously by the experimenter.

Procedure

Subjects made a dental impression on wax affixed to a bite bar. Infrared spectacles were worn and secured with an elastic band placed around the head. Subjects were seated in front of the video monitor and placed their mouths on the bite bar. The background luminance (0.1 cd/m^2) and stimuli size (1° of visual angle, within which was a small central spot subtending a few minutes of arc) and luminance (1.6 cd/m^2) remained constant throughout testing. Prior to each task, subjects were presented with calibration targets at central fixation and ±5, 10, 15, 17.5, and 20°.

Refixation saccade tasks. For the visually guided centrifugal/centripetal saccade task, the target began at central fixation. After a pseudorandom 1.5–2.0-s interval, the target jumped to one of eight possible locations: ±5, 10, 15, or 20° (the stimulus for a centrifugal saccade). After a 1.5-s interval, the target jumped pseudorandomly to one of the remaining three possible locations on the same side of the screen. Following a pseudorandom 1.5–2.0-s interval, the target jumped back to the central fixation point (the stimulus for a centripetal saccade), where it remained for 1.5 s before the beginning of a new sequence. The current fixation point was extinguished simultaneously with the illumination of the new target. The completed task required subjects to generate five saccades to each target amplitude in each direction for both centrifugal and centripetal movements. Subjects were told to follow the target as closely as possible.

For the visually guided midpoint saccade task, the target started at one of 16 different target locations: ±2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, or 20.0° from central fixation. After a 1.5–2.0-s pseudorandom interval, the new target appeared on the opposite side of the screen (e.g., from 7.5° left to 7.5° right). After a 1.5-s interval, the target jumped pseudorandomly to one of the remaining seven possible target locations on the same side of the screen before the beginning of a new sequence. Again, the current fixation point was extinguished simultaneously with the illumination of the new target. The completed task required subjects to generate five saccades for each target amplitude (5, 10, 15, 20, 25, 30, 35, and 40°) in each direction. Subjects were instructed to follow the target as closely as possible.

Predictive saccadic tracking tasks. A target alternated at 0.4 Hz between the ±15° target locations. Subjects were told that the target would move in a predictable fashion and were instructed to keep their eyes on the target as much as possible. Three predictive tracking conditions were used: (a) in the regular condition, the old target was extinguished simultaneously with the illumination of the new target; (b) in the gap condition, the old target was extinguished 250 ms prior to the illumination of the new target; and (c) in the overlay condition, blue target-sized dots were continuously present at the ±15° positions. A luminescent yellow target overlaid the blue dots at 0.4 Hz. Sixteen cycles were presented for each of the three conditions. Order of presentation for the three predictive tracking conditions was counterbalanced within groups.

Ocular Motor Analyses

Waveforms were displayed using ASYST (Version 4.0; Keithley Instruments, Inc.). Digitized data were low-pass filtered in the frequency domain at 60 Hz. For each trial, the position, velocity, and acceleration arrays were presented simultaneously on a high-resolution color monitor. Only trials free of artifact were scored. Values were calculated separately for each eye.

Our infrared recordings are linear through approximately ±16°; degree of visual angle per number of digital units is typically a decelerating function for more extreme values (i.e., when predicting degree of visual angle from digital units, the function is sigmoid in shape). To change accurately digital units into degrees of visual angle, we calculated 1st–5th order polynomials and visually inspected their fit to the fixation data. Digitized ocular motor data were then transformed to degree of visual angle via application of the "best-fitting" function (typically either cubic or quintic).

Saccade scoring. For each saccade, the event was bracketed by the scorer, and reaction time (milliseconds between target movement and eye velocity increase above 10°/s, defined as the beginning of the saccade; cf. Abel et al. 1983, p. 34), saccade duration (milliseconds between the eye velocity increase above 10°/s and the subsequent decrease below 10°/s, defined as the end of the saccade), amplitude (degree of visual angle traversed from the beginning to the end of the saccade), and peak velocity (highest degree/second value attained during the saccade) were automatically computed. For the visually guided refixation saccade tasks, only saccades with reaction times greater than 90 ms and with saccadic gains (saccade amplitude/target amplitude) greater than 0.20 were included in the following analyses. The predictive saccade tasks were divided into five successive blocks (three cycles in each block, excluding the first cycle). This allowed us to evaluate whether subjects developed a predictive strategy over trials. Because it was extremely difficult to distinguish small intrusive and corrective saccades from extremely

hypometric refixation efforts, only saccades >3° of visual angle in the direction of target motion were scored. The first scorable event in the direction of target motion occurring in the interval between 1,000 ms before to 1,000 ms after the target jump was evaluated.

Results

Data Analyses

Analysis of main and interaction effects. For all analyses, we maintained the familywise Type I error rate at 0.05 by applying a stagewise procedure for multiple comparisons (Holland & Copenhaver, 1988), and we calculated effect sizes using the standard deviation of the nonpsychiatric group in the denominator (Smith, Glass, & Miller, 1980). For the refixation tasks, we calculated mean square correlations using the Statistical Analysis System's (SAS) NESTED procedure (Statistical Analysis Institute, 1988) to determine how tightly yoked the two eyes were on the saccade variables. We tested for between-group differences on these correlations using Fisher's Z transformation. For all tasks, when there were not strong a priori predictions about theoretical functions for the data distributions, we used the following procedures. If there was not a repeated-measures factor, we used analyses of variance (ANOVAs) or t tests. If there were main or interaction effects involving a repeated-measures factor (including, where appropriate, the analysis of simple main effects), we used a multivariate ANOVA (MANOVA) approach (Vasey & Thayer, 1987). When appropriate, we used Helmert contrasts and t tests to follow-up statistically significant effects.

Weighted least-squares regressions. Based on the results of previous investigations, it was possible to make strong predictions about the within-subject relationships between variables used in the present study: a linear relationship between saccadic amplitude and target amplitude (Becker, 1989, p. 33), an exponential relationship between saccadic peak velocity and saccadic amplitude (Leigh & Zee, 1991, p. 80), and a linear relationship between saccadic duration and saccadic amplitude (Leigh & Zee, 1991, p. 80). Part of our analyses, therefore, consisted of fitting theoretical equations to experimental data.

The typical method used to fit a theoretical equation to experimental data involves adjusting the equation's free parameters until the sum of the squared deviations between the predicted and observed values is minimized. The procedure involves minimizing $\Sigma(y_i' - y_i)^2$, where y_i' is the predicted value and y_i is the observed value. This simple approach is legitimate when each of the values being fit is measured with the same degree of precision (i.e., when the variance associated with each y_i is the same). In many cases, values of σ_i^2 are widely discrepant from point to point. Under these conditions, weighted least squares is the appropriate procedure (Bevington, 1969).

If the data points to be fit each represent a single observation from a population with known variance, σ_i^2, then each squared deviation should be weighted by $1/\sigma_i^2$ (the reciprocal of the known variance for the data point i). Thus, the value minimized is $\Sigma(y_i' - y_i)^2/\sigma_i^2$ (deviations from imprecisely determined points—those with large values of σ_i^2—are given less weight than deviations from more precisely determined points—those with small values of σ_i^2). As a result, the fitting procedure yields more valid estimates of the equation's parameters than would be obtained using unweighted least squares. Indeed, assuming Gaussian error distributions, the weighted least squares procedure yields maximum likelihood parameter estimates (Bevington, 1969).

In the fits performed below (using the minimization routine described by Bevington, 1969), the data points were not single observations, and the population variances were not known a priori. Instead, each point represented the mean of multiple observations, and the uncertainty associated with each mean was estimated from the obtained squared standard error. Maximum likelihood parameter estimates can be obtained under these conditions by weighting each squared deviation (which now refers to the deviation between observed and predicted means) by the reciprocal of the squared standard error of the mean (s_i^2/n_i, where s_i^2 represents the variance of the observations and n_i represents the number of observations used to compute a given point). Thus, the value minimized is $\Sigma n_i(\bar{y}_i' - \bar{y}_i)^2/s_i^2$, where $\bar{y}_i$ represents an observed mean value and $\bar{y}_i'$ represents a predicted mean value.

Refixation Saccade Tasks

Visually guided centrifugal/centripetal saccade task. As described in the introduction, the variables of theoretical interest from the centrifugal/centripetal saccade task were reaction time and amplitude. We evaluated for effects of target direction on these variables using a Group (schizophrenia, nonpsychiatric) × Target Direction (left, right) × Target Amplitude (5, 10, 15, and 20°) × Target Type (centrifugal, centripetal) MANOVA. There were no statistically significant effects of target direction involving group membership on any of the centrifugal/centripetal saccade variables. As a result, the following analyses are presented collapsing over target direction.

Data from both eyes were available for 20 schizophrenia patients and 22 nonpsychiatric subjects. The between-eye mean square correlations for the two groups are presented in Table 1. As can be seen by inspection of these correlations, the eyes were reasonably tightly yoked. There were also no statistically significant differences between groups on these correlations. The remaining centrifugal/centripetal saccade analyses, therefore, were conducted using averages of the two eyes for subjects with available data from both eyes. For the remaining subjects, data from the available eye (either right or left) were used.

Table 1. *Between-Eye Mean Square Correlations During Visually Guided Refixation Saccade Tasks*

	Group	
Variable	Schizophrenic	Nonpsychiatric
Centrifugal saccades		
Reaction time	.993	.998
Amplitude	.735	.799
Centripetal saccades		
Reaction time	.998	.994
Amplitude	.700	.831
Midpoint saccades		
Reaction time	.996	.998
Amplitude	.716	.648
Duration	.954	.939
Peak velocity	.740	.629

We analyzed for group differences on saccadic reaction time and saccade amplitude using a Group (schizophrenia, nonpsychiatric) × Target Amplitude (5, 10, 15, and 20°) × Target Type (centrifugal, centripetal) MANOVA. There were no significant main or interaction effects involving group membership on reaction time. The mean saccadic reaction time across target conditions for schizophrenia patients was 174.4 ms ($SD = 21.6$). The mean saccadic reaction time for nonpsychiatric subjects was 166.1 ms ($SD = 20.4$). There were also no significant effects involving group membership on saccade amplitude (see Table 2).

Visually guided midpoint saccade task. We evaluated for effects of target direction on reaction time, duration, amplitude, and peak velocity using a Group (schizophrenia, nonpsychiatric) × Target Direction (left, right) × Target Amplitude (5, 10, 15, 20, 25, 30, 35, and 40°) MANOVA. There were no statistically significant effects of target direction involving group membership on any of the midpoint saccade variables. As a result, the following analyses are presented collapsing over target direction.

Data from both eyes were available for 18 schizophrenia patients and 23 nonpsychiatric subjects. The between-eye mean square correlations for the two groups are presented in Table 1. Again, inspection of these correlations indicated that the eyes were reasonably tightly yoked. There were also no statistically significant differences between groups on these correlations. The remaining midpoint saccade analyses, therefore, were conducted using averages of the two eyes for subjects with available data from both eyes. For the remaining subjects, data from the available eye (either right or left) were used.

We analyzed for group differences on saccadic reaction time, saccade amplitude, the relationship between saccadic peak velocity and saccade amplitude, and the relationship between saccade duration and saccade amplitude. For reaction time, we used a Group (schizophrenia, nonpsychiatric) × Target Amplitude (5, 10, 15, 20, 25, 30, 35, and 40°) MANOVA. The remaining analyses were conducted using weighted least squares regressions. The functions were fit for each individual subject and the resulting individual parameter estimates were used to test for group differences.

Table 2. *Mean (SD) Saccade Amplitude by Target Location for Centrifugal and Centripetal Saccades*

	Group		
Variable	Schizophrenic	Nonpsychiatric	Effect size[a]
Centrifugal			
5°	4.8 (0.71)	4.9 (1.00)	−0.10
10°	9.2 (1.09)	9.3 (1.33)	−0.08
15°	13.6 (1.41)	13.6 (1.49)	0.00
20°	17.7 (1.61)	17.2 (2.09)	0.24
Centripetal			
5°	4.7 (0.64)	4.8 (0.98)	−0.10
10°	9.5 (1.12)	9.4 (1.53)	0.07
15°	14.4 (1.63)	14.7 (1.88)	−0.16
20°	18.3 (2.09)	18.1 (3.27)	0.06

[a]A negative effect size indicates that schizophrenia patients had a smaller mean than the nonpsychiatric subjects.

There were no significant effects involving group membership on reaction time. The mean saccadic reaction time across target conditions for schizophrenia patients was 181.7 ms ($SD = 22.4$). The mean reaction time for nonpsychiatric subjects was 173.0 ms ($SD = 21.3$).

To evaluate for group differences on saccade amplitude, we used a linear function of the form $y' = bx + a$, where y' is the predicted saccade amplitude, b is the slope, x is target amplitude (5, 10, 15, 20, 25, 30, 35, and 40°), and a is the y-intercept (see Figure 1A). There were no statistically significant between-group differences on slopes (schizophrenia $M = 0.86$, $SD = .068$; nonpsychiatric $M = 0.87$, $SD = .073$) or y-intercepts (schizophrenia $M = 0.90°$, $SD = 0.80$; nonpsychiatric $M = 0.42°$, $SD = 0.67$).

We next investigated the relationship between saccadic peak velocity and saccadic amplitude (see Figure 1B) using an exponential function of the form $y' = V_{max} * [1 - \exp^{(-x/C)}]$, where y' is the predicted saccadic peak velocity, V_{max} is the estimated asymptotic peak velocity, x is the saccadic amplitude, and C is the rate constant. There were no statistically significant between-group differences on asymptotic peak velocity (schizophrenia $M = 586.1$°/s, $SD = 104.7$; nonpsychiatric $M = 558.7$°/s, $SD = 94.9$) or rate of approach (schizophrenia $M = 13.8°$, $SD = 3.1$; nonpsychiatric $M = 14.4°$, $SD = 3.4$).

Finally, we evaluated the relationship between saccade duration and saccadic amplitude (see Figure 1B) using a linear function of the form $y' = bx + a$, where y' is the predicted saccade

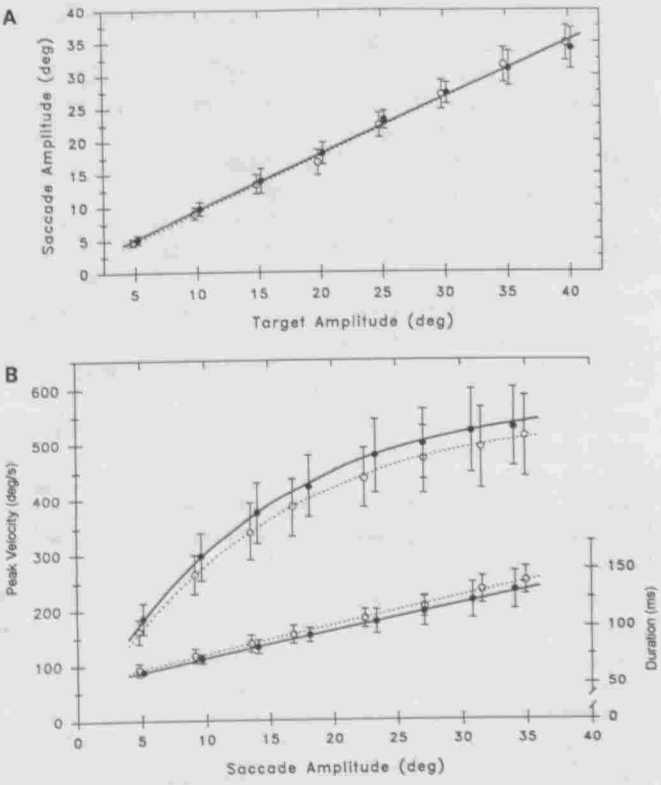

Figure 1. Means and standard deviations from the visually guided midpoint saccade task for (A) the relationship between target amplitude and saccade amplitude for schizophrenia patients (filled symbols, solid line) and nonpsychiatric subjects (hollow symbols, dashed line) and (B) the relationship of saccade amplitude to peak velocity and duration for schizophrenia patients (filled symbols, solid lines) and nonpsychiatric subjects (hollow symbols, dashed lines).

duration, b is the slope, x is the saccadic amplitude, and a is the y-intercept. There were no statistically significant between-group differences on slope (schizophrenia $M = 2.37$ ms/degree, $SD = 0.48$; nonpsychiatric $M = 2.53$ ms/degree, $SD = 0.44$), or y-intercept (schizophrenia $M = 48.9$ ms, $SD = 4.3$; nonpsychiatric $M = 50.5$ ms, $SD = 6.7$).

Predictive Saccadic Tracking

Predictive saccade metrics. Because the left and right eyes were reasonably tightly yoked in the previous saccade paradigms, we again used the average of two eyes (17 schizophrenia patients and 25 nonpsychiatric subjects had data from both eyes available). We analyzed for group differences on saccadic reaction time and saccadic amplitude using a Group (schizophrenia, nonpsychiatric) × Direction (left, right) × Block (first, second, third, fourth, and fifth) × Type (gap, regular, and overlay) MANOVA. For reaction time, there was a main effect of block, Wilks's lambda = .53, $F(4,46) = 10.1$, $p < .001$. Reaction time during the first block was slower than during the remaining blocks (Helmert contrasts). There was also a main effect of type, Wilks's lambda = .15, $F(2,48) = 136.8$, $p < .001$. Reaction times during the gap task were faster than reaction times during the regular and overlay tasks, and reaction times during the regular task were faster than reaction times during the overlay task (Helmert contrasts). Finally, there was an effect of group membership, $F(1,49) = 5.0$, $p = .030$. The schizophrenia patients had significantly faster reaction times than the nonpsychiatric subjects (see Table 3 and Figure 2).

Regarding amplitude, there was a main effect of type, Wilks's lambda = .36, $F(2,48) = 43.5$, $p < .001$. Saccadic amplitudes during the gap task were significantly shorter than saccadic amplitudes during the regular and overlay tasks, and saccadic amplitudes during the regular task were shorter than saccadic amplitudes during the overlay task (Helmert contrasts). In addition, there was an effect of group membership, $F(1,49) = 6.4$, $p = .015$. Schizophrenia patients executed significantly smaller, or hypometric, saccades (see Table 3 and Figure 2).

The relationship between saccadic amplitude and saccadic reaction time. During predictive tracking, schizophrenia patients produced faster reaction time and shorter amplitude saccades than nonpsychiatric subjects. To evaluate for between-group differences on amplitude as a function of reaction time during predictive saccadic tracking, we used the following exploratory procedure. First, because there were no statistically significant Group × Type (gap, regular, overlay) interactions on either reaction time or amplitude, we used all saccades regardless of type. Second, we formed 13 125-ms reaction time bins (the lower limit of the earliest bin was 875 ms before new target appearance and the upper limit of the latest bin was 750 ms after target appearance). Third, using all saccades generated within a group (schizophrenia, nonpsychiatric), we calculated the average reaction time, average amplitude, and squared standard error around the average amplitude within each bin. We then plotted the saccadic amplitudes as a function of reaction time for both groups (see Figure 3).

For both groups, the distribution of amplitudes as a function of reaction times had the characteristic shape of a logistic function (i.e., a period of lower amplitudes prior to about −200 ms, a transition period between −200 and 200 ms, and a period of higher amplitudes after 200 ms). To determine whether there were between-group differences in function characteristics, we fit the following equation (using weighted least-squares) to each group's data:

$$y' = \frac{b * [1 - \exp(-a * x)]}{1 + \exp(-a * x)} + c,$$

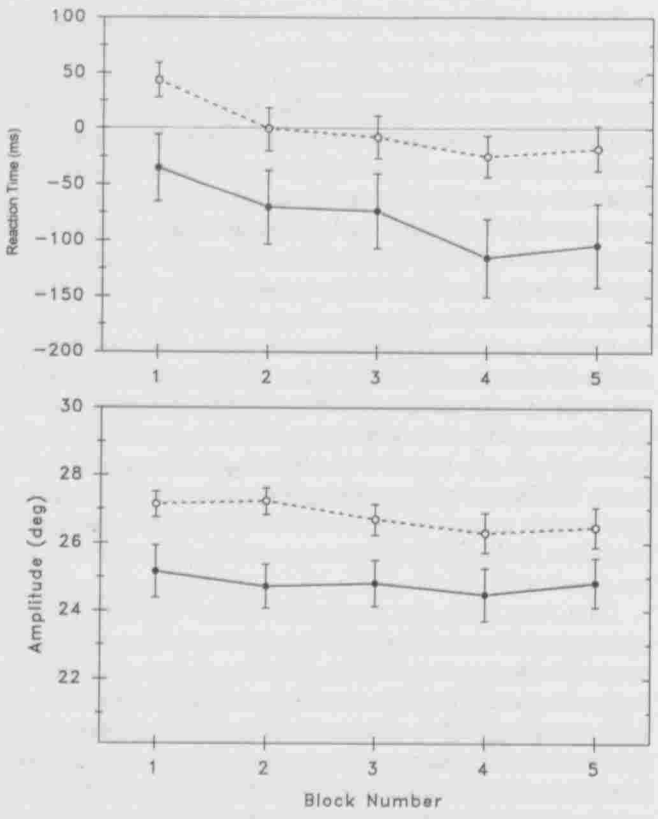

Figure 2. Means and standard errors during the predictive saccadic tracing task of the reaction times and amplitudes over blocks of trials for schizophrenia patients (filled symbols, solid lines) and nonpsychiatric subjects (hollow symbols, dashed lines). The dashed line at 0 ms in the reaction time plot indicates the time of new target illumination. The size of the target displacement was 30°.

Table 3. *Mean (SD) Reaction Times and Amplitudes by Type of Stimulus Condition for the Predictive Saccadic Tracking Tasks*

Variable	Group: Schizophrenic	Group: Nonpsychiatric	Effect size[a]
Average reaction time (ms)			
Gap	−217.0 (148.6)	−133.5 (95.9)	−0.87
Regular	−84.3 (146.9)	21.6 (85.9)	−1.23
Overlay	61.9 (220.8)	108.0 (126.1)	−0.37
Average amplitude (degree)			
Gap	22.7 (4.3)	25.2 (2.8)	−0.89
Regular	24.1 (3.2)	26.7 (2.6)	−1.00
Overlay	27.6 (3.6)	28.4 (2.3)	−0.35

[a]A negative effect size means that schizophrenia patients had a smaller mean than nonpsychiatric subjects.

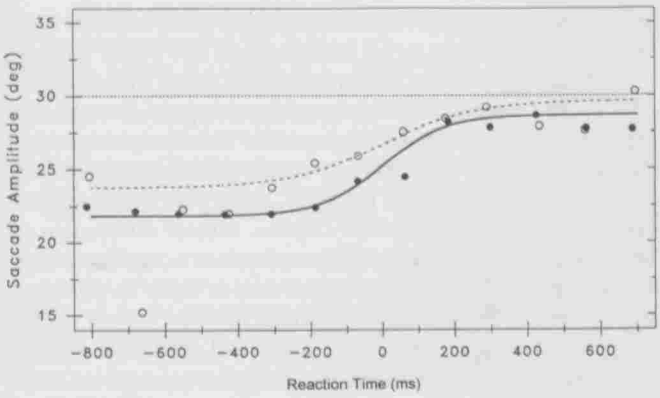

Figure 3. A logistic transition function derived from the predictive saccadic tracking data of saccadic amplitude on reaction time for schizophrenia subjects (filled symbols, solid line) and nonpsychiatric subjects (hollow symbols, dashed line). The shape of the function did not significantly differ between groups, but the curve for the schizophrenia patients was shifted significantly downward, indicating hypometria of saccades across reaction times.

where y' is saccadic amplitude, a is the rate of transition from the lower to the upper asymptote (smaller values indicated a relatively slow transition; larger values indicated a relatively fast transition), b is half the amplitude difference between the lower and upper asymptotes (smaller values indicated that the asymptotes were closer together; larger values indicated that they were farther apart), c is distance (in degrees) between the abscissa and the amplitude midpoint of the function (a variable roughly analogous to the y-intercept), and x is saccadic reaction time in seconds (the reaction times were in seconds rather than milliseconds to reduce convergence difficulties). After obtaining the optimal within-group parameter estimates, the standard errors around each parameter were bootstrapped by fixing the other two parameters at their optimal values, sampling with replacement to $n = 13$ (the number of reaction time bins), fitting the function, and repeating this process 1,000 times (Wasserman & Bockenholt, 1989).

We used t tests to compare the parameter estimates between groups (Ratkowski, 1983). There were no significant group differences on the a (schizophrenia estimate = 11.65, $SE = 2.30$; nonpsychiatric estimate = 7.76, $SE = 1.58$) or b (schizophrenia estimate = 3.40, $SE = 0.28$; nonpsychiatric estimate = 2.96, $SE = 0.14$) parameters, $ts < 1.41$, $ps > .05$. These results indicated that the shape of the logistic function did not differ between groups. The c parameter, however, did differ significantly between-groups, $t = 7.92$, $p < .001$. This result indicated that the height of the function above the abscissa was significantly lower for the schizophrenia patients ($c = 25.24°$, $SE = 0.18$) than for the nonpsychiatric subjects ($c = 26.70°$, $SE = 0.04$), regardless of saccadic reaction time.

Discussion

Schizophrenia patients performed visually guided refixation saccades like nonpsychiatric subjects and learned to anticipate target motion during saccadic tracking tasks. Regardless of the type of square wave paradigm presented, both schizophrenia and nonpsychiatric subjects decreased reaction times over blocks of consecutive trials. Schizophrenia patients, however, produced both faster reaction time and shorter amplitude saccades than nonpsychiatric subjects during predictive tracking. These findings may have implications for understanding the neuropathological substrate(s) of ocular motor abnormalities among schizophrenia patients.

Refixation Saccade Task Results

Visually guided refixation saccade metrics (measured from both centrifugal/centripetal and midpoint tasks) did not differ between schizophrenia and nonpsychiatric subjects. The two groups had similar between-eye correlations on the saccadic variables, a finding inconsistent with cerebellar dysfunction in schizophrenia (Vilis, Snow, & Hore, 1983). The between-group similarities on centrifugal/centripetal saccade amplitudes also suggest that the cerebellum's saccade-related regions are not impaired among schizophrenia patients. Both humans with cerebellar disease and monkeys with experimental cerebellar lesions show hypometric centrifugal and hypermetric centripetal saccades (Leigh & Zee, 1991), a pattern not observed among the schizophrenia patients. The midpoint saccade data demonstrated that schizophrenia and nonpsychiatric subjects had similar saccadic reaction times, saccadic amplitudes, and relationships between peak velocity and amplitude and between duration and amplitude. These results may indicate that brainstem saccade-generating mechanisms (Leigh & Zee, 1991) are functioning normally among schizophrenia patients (see also Clementz et al., 1994). The visually guided refixation results, therefore, suggest that schizophrenia patients do not have a general problem with saccade generation.

Predictive Saccadic Tracking Results

The predictive saccadic tracking results seem to be inconsistent with the hypothesis that FEF pathology contributes to saccadic abnormalities among schizophrenia patients. The extant data suggest that FEF pathology should result in the inability to reduce saccadic reaction times over trials (Bruce & Borden, 1986) and in difficulty generating saccades that anticipate target motion (Braun et al., 1992). Schizophrenia patients did not appear to have either anomaly. In fact, schizophrenia patients produced faster reaction time saccades during predictive tracking than nonpsychiatric subjects.

Given that the schizophrenia patients were taking dopamine antagonists, the possibility that decreased saccadic reaction times can be secondary to drug treatment must be considered. Interestingly, there is no evidence that dopamine antagonists decrease saccadic reaction times. In fact, dopamine antagonists might be expected to have the opposite effect: Parkinson's disease patients are slow to develop a predictive strategy (Crawford et al., 1989), have increased saccadic reaction times with increased disease severity (Rascol et al., 1989), and show modest decreases in saccadic reaction times with L-Dopa administration (Rascol et al., 1989). Subjects with MPTP lesions have decreases in saccadic reaction times with dopamine replacement therapy (Hotson, Langston, & Langston, 1986). Finally, dopamine antagonists injected directly into monkey prefrontal cortex result in increased saccadic latencies for memory-guided but not visually guided saccades (Sawaguchi & Goldman-Rakic, 1994). Medicated schizophrenia patients, ceteris paribus, might have been expected to demonstrate slower reaction time saccades during predictive tracking than nonpsychiatric subjects. Thus, the reaction time results are not easily attributable to antipsychotic medication effects.

Schizophrenia patients also had hypometric saccades relative to nonpsychiatric subjects. An excess of fast reaction time saccades (many of which would be made before new target illumination) might be expected to result in hypometric saccades (anticipatory saccades tend to have shorter amplitudes than visually guided saccades; see Smit & Van Gisbergen, 1989). A logistic function relating amplitude to reaction time during square wave tracking, however, indicated that schizophrenia patients generated hypometric saccades regardless of reaction time. This function did not significantly differ in shape between schizophrenia and nonpsychiatric subjects, it was simply shifted downward along the amplitude axis for the schizophrenia patients.

The saccadic hypometria observed among the schizophrenia patients must also be considered with respect to treatment with antipsychotic medication. In fact, there is ample evidence that dopamine antagonists may result in decreased saccadic amplitudes during predictive saccadic tracking. Medicated schizophrenia patients have hypometric saccades during predictive tracking compared with both unmedicated schizophrenia patients and nonpsychiatric subjects (Hommer et al., 1991). Parkinson's patients have hypometric anticipatory and memory-guided saccades (Crawford et al., 1989) but accurate visually guided saccades (Ventre, Zee, Papageorgiou, & Reich, 1992). Patients with MPTP lesions generate hypometric saccades that are increased in amplitude by dopamine replacement therapy (Hotson et al., 1986). Finally, dopamine antagonists injected into monkey prefrontal cortex result in less accurate memory-guided saccades without affecting visually guided saccades (Sawaguchi & Goldman-Rakic, 1994). The observed pattern among schizophrenia patients of accurate visually guided saccades and hypometric saccades during predictive tracking may be attributable to an antipsychotic medication effect.

Hommer et al. (1991) specifically suggested that hypometric anticipatory saccades during predictive tracking indicate a "failure of working memory" in schizophrenia (cf. Goldman-Rakic, 1987). However, our data suggest that during square wave tracking, both schizophrenia patients and nonpsychiatric subjects generate relatively small saccades when reaction times are faster (before new target illumination), and bigger saccades when reaction times are slower (after new target illumination). This pattern suggests that hypometric anticipatory saccades during predictive tracking are not specific to schizophrenia, and their presence may not carry any special neuropathological significance for this disorder. However, there were trends suggesting that schizophrenia–nonpsychiatric subject differences on both saccadic reaction time and amplitude are considerably reduced, but not eliminated (see effect sizes in Table 2), during an overlay task (when reliance on working memory should be considerably attenuated). Future research will determine whether this pattern has any significance for the failure of working memory hypothesis.

Conclusion

The current study provides evidence that is inconsistent with the hypothesis that FEF pathology is related to ocular motor abnormalities observed among schizophrenia patients. Decreased saccadic reaction times during predictive tracking among schizophrenia patients may be consistent with a failure of inhibition, typically attributed to dysfunction of dorsolateral prefrontal cortex and/or its related subcortical neural circuitry (e.g., Alexander, Crutcher, & DeLong, 1990; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991). This hypothesis might be evaluated by manipulating the oscillation frequency of square wave presentations. Ross and Ross (1987) reported that, in a sample of normal subjects, frequencies slower than approximately 0.4 Hz resulted in fewer anticipatory saccades. If faster reaction time saccades during predictive tracking are related to inhibitory failure among schizophrenia patients, then slower oscillation frequencies should lead to an increased frequency of anticipatory saccades in this population: increased interstimulus intervals should increase the probability of generating an anticipatory movement. We are currently testing this hypothesis.

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(Received July 21, 1994; Accepted March 15, 1995)